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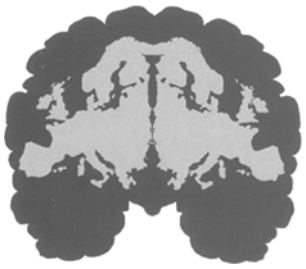

The European Brain Injury Consortium

Nemo solus satis sapit: Nobody Knows Enough Alone

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Introduction

The need for international collaboration in the conduct of research in the clinical management of head injury has never been greater. Rigorous evaluation must be carried out on a range of approaches that include new pharmacological agents – so-called neuroprotective drugs, manipulations of physiological conditions, eg hypothermia, and protocols for aspects of management ranging from initial resuscitation and triage to details of intensive care – "guidelines".

The European Brain Injury Consortium has been formed to promote international, multicentre, interdisciplinary research aimed at improving the outcome of patients who have suffered a head injury or other kind of acute brain damage. This article describes the origin, nature and aims of the organisation and its initial activities and achievements.

Background

The increased understanding of mechanisms of brain damage and the development of specific, targeted treatments has drawn the interest of many agencies. Much of the interest has been focused on ischaemic brain damage and many neuropharmacological agents have been shown to reduce the amount of damage occurring after insults induced experimentally in the laboratory (McIntosh 1993 [21], Korshitz 1996 [13]). Interest in applying such treatments to head injuries stems from the highlighting of the frequency of secondary insults (Miller 1978 [22]) of an ischaemic nature and their importance in determining outcome (Jones 1994 [12], Gopinath 1994 [8]) and the evidence that at the molecular, cellular level, the mechanisms of ischaemia and trauma merge (Jenkins 1989 [9], Cohadon 1994 [5]). Moreover, because head injuries are treated urgently and usually monitored intensively, they are a more appropriate population than stroke victims in which to carry out early research in so-called neuroprotective treatments (Teasdale and Bannon 1997 [26]).

Many of the new approaches stem from extensive development programmes conducted by pharmaceuti-

cal companies. Often, head injury is a new area for a company which thus lacks "in-house" expertise about such crucial factors in clinical trials as the selection of patients to study, the data to collect, and the way to assess outcome. Thus, the lack of experience may extend to knowledge of the appropriate sources for advice, leading to a temptation to contact clinicians because they are either geographically convenient or have previously collaborated in another area of research. Understandable enthusiasm, unhindered by experience and understanding of research in the management of head trauma, has led to instances of protocols being developed in detail before they have been presented for general scrutiny. The ensuing conflicts between protocols that are "set in stone" and the wisdom and knowledge of experienced investigators about what will actually work in practice, can lead at best to frustration and irritation, at worst to conflict and impasse. The need to avoid and to deal with these tensions and to bring a strong, independent clinical, scientific perspective to the conduct of research in this field, led in 1994 to the development of consortia of investigators in North America (Marmarou 1996 [16]) and Europe. This article describes the evolution and initial activities of the European Brain Injury Consortium.

Precedents

The formation of the European Association of Neurosurgical Societies in 1971 promoted clinical and scientific contacts and discussions between European neurosurgeons. The institution by the World Federation of Neurosurgical Societies of an "ad hoc" Committee on Head Injuries in 1965 followed by the establishment of a Committee of Neuro-Traumatology in 1977, provided a worldwide focus on the problems of neurotrauma. Some of the first fruits of international co-operation took the form of retrospective studies of cohorts of patients, typified by the comparative Scottish/Dutch studies of patients with compound depressed fracture (Braakman and Jennett 1975 [2]). Scottish and Dutch centres were also involved with centres in the west coast of America in early prospective international studies, the so-called International Traumatic Coma Data Bank (Jennett 1977 [11], Murray 1986 [24]). These studies led to the development of methods of description of severity of injury (Teasdale and Jennett 1974 [27]), and of assessing outcome (Jennett and Bond 1975 [10]), that became standards (Langfitt 1978 [14]) for subsequent studies. The North American Traumatic Coma Data Bank (Marshall 1983 [17]) aimed to explore in greater depth and detail the pathophysiology of the acute stage, for example in regard to intracranial pressure, cerebral perfusion pressure, secondary insults, and CT scan classification and their relations to outcome (Marshall 1991 [18]).

The methods developed in the foregoing observational studies (Miller and Teasdale 1985 [23]) were applied to local and national trials (e.g., Braakman 1983 [3]), and then to a prospective randomised international control trial of a calcium antagonist in severe head injuries by a British/Finnish group (Bailey *et al.* 1991 [1]). This study showed a trend to benefit but the population studied was insufficient for adequate statistical power. The performance of a further study required the involvement of a larger number of units in more European countries (The European Collaborative Study of Nimodipine 1994 [28]). This study recruited 852 patients in 21 units in 13 countries and proved the feasibility of multi-centre, multinational European collaborative trials while also providing insights into their problems.

The Gestation of "EBIC"

The concept of an European organisation was proposed at a meeting held on 1st October 1993 in London. Although composed principally of investigators from British neurosurgical and neurointensive care units, the meeting was also attended by representatives from other European countries. There was a clear consensus that, while individual countries should continue internal collaborations, the overriding priority was for an European-wide organisation. This reflected the realisation that the numbers of patients required in the design of definitive Phase III studies of severe head injury demanded European-wide recruitment. It also reflected the perception that an organisation of this scope and scale – both in terms of numbers of centres and expertise of investigators – would be able to conduct fruitful negotiations on crucial scientific factors with multinational pharmaceutical companies and other sponsors of research.

The first preparatory meeting for the European-wide organisation was held in Amsterdam on 5th February 1994. Invitations were issued to neurosurgeons and neurointensivists who were known to have an interest in research in head injuries, either because they had participated in previous studies, or had a record of publication and research. The meeting was

attended by representatives from 40 centres in 10 countries who agreed to set up a small working party to prepare and report on further plans. At a second meeting on 19th March 1994 these provisional proposals were endorsed and the meeting charged a steering committee with the duty of bringing back detailed proposals for formal deliberation at the time of the meeting of the European Association of Neurosurgical Societies in 1995. In the meantime, the steering committee were authorised to initiate discussions and planning for scientific activities. The steering committee's proposals were presented to a meeting in Berlin on 9th May 1995 attended by 36 neurosurgeons and neurointensivists from 10 countries. After thoughtful and serious discussion, the proposals were accepted and the European Brain Injury Consortium became formally constituted.

The Aims of "EBIC"

1. To promote and to conduct research aimed at improving the outcome of patients with acute brain injury; to bring a strong, independent clinical perspective to the evaluation of new treatments.
2. To establish close co-operation between European head injury centres and investigators in the management of severe head injury and other types of acute brain damage.
3. To negotiate with, and to work in partnership with sponsors to ensure excellence in the design, conduct, analysis and publication of clinical trials in neuroprotection.
4. To act as an advisory organ both in practical and theoretical issues concerning all kinds of brain injury studies.

Structure

It was recognised that an informal, loose association would no longer serve to meet the challenges and responsibilities of the new organisation. This was not least because there was a need to develop a clear identity, focus, and status in discussions and negotiations with outside bodies. At the same time, there was a desire to avoid an overly formal, rigid structure with excessive administrative encumbrances. There was also recognition that although the organisation should be wide-spread throughout Europe, the reality was that levels of interest and commitment to head injury research varied and that a strictly geographically/politically representative structure was both inappropriate and even potentially divisive.

The reference to the organisation as a "Consortium" came after considerable discussion and even consultation with the Oxford English Dictionary which defined a Consortium as a temporary co-operation of several powers or large interests to effect some common purpose. The term seemed preferable to other choices such as Society, Co-operative or even Cartel! It reflected also the development of many similarly termed groups in various aspects of medicine. A search of a database (Bath Information and Data Services) in January 1997 disclosed references to 39 medical consortia, those in the neurosciences include genetics, muscular dystrophy, stroke, epilepsy, brain tumours and dementia.

The steering committee of the Consortium received strong legal advice that, whatever the organisation's title or structure, it could be seen as acting as an identifiable body, incurring responsibilities and liabilities that could fall on each individual who in any way participated in its activities. The steering committee therefore accepted the advice that the Consortium should establish itself as a registered company, number SC159579, with the liabilities of the individual members of the company limited by guarantee to a maximum sum of £1. Furthermore, it was proposed and accepted that the required named directors and members of such a company should consist of participants in the then steering committee or their successors in the Executive of the Consortium. The benefits of these arrangement were seen to be the avoidance of potential personal financial liability, the establishment of EBIC as a legally recognised body, able to form agreements with other bodies of a more formal nature, and the removal of the need to identify by name each individual potentially participating in activities of the Consortium. These were considered to outweigh the potential disadvantages in terms of formalisation and organisational complexity. An additional advantage, recently achieved, has been that the organisation has been able to apply successfully for recognition as a Scottish Charity (No SC025721).

The aim in the establishment of the organisational structure and the central Executive of the Consortium was to facilitate co-operation and communication amongst the wider membership, both between individual centres and between them and potential sponsors of studies. In order to achieve this, the Consortium has established a central co-ordinating centre, with an administrator, based in the University of Glasgow. The administrator is responsible for communication with members, including regular newslet-

ters, and for organisation of meetings of the Executive, which have been held at 1–2 month intervals through 1995 and 1996. Detailed initial discussions about potential projects are conducted by the Executive, for each potential study a specific working party is set up, whose aim is to draw up a suitable scientific protocol for presentation to members. On the other hand, it is a principle of the Consortium that negotiations regarding the participation of an individual centre in the study are conducted directly between the representatives of that centre and the sponsor, and formalised in a contract between these parties without the intervention of the Consortium.

Membership

Investigators from over 120 centres in 22 countries have expressed an interest in participating in the activities of EBIC (Fig. 1, Appendix 1). In accord with the foregoing organisational structure, no attempt so far has been made to establish criteria for centres which are "members". On the other hand, the realities of research, in particular its sources of funding, have meant that so far is has not been possible for all interested centres to have become "active" centres. Pharmaceutical companies, in particular, have strong preferences for carrying out research in particular countries or regions. This reflects considerations that include the sponsor's pre-existing infrastructure and the time factors involved in regulatory processes in different parts of Europe, as well as the capabilities of a centre for studies of varying technological complexity.

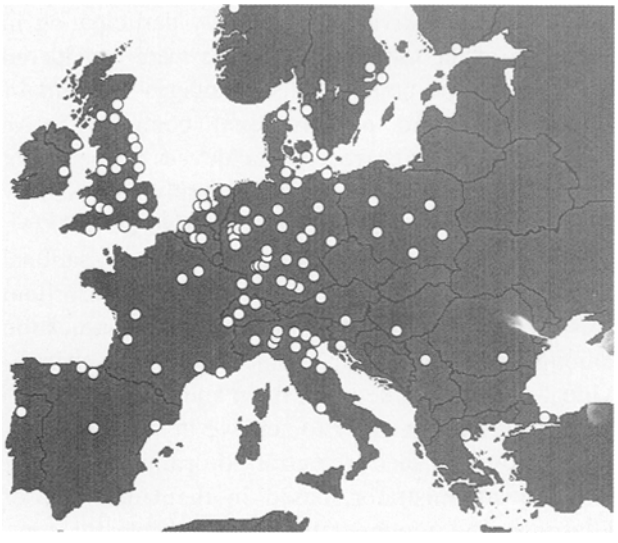

Fig. 1.

Core Data Study

The feasibility of collaborative research in such a large number of European centres was tested in a "Pilot Core Data Study". A two page proforma was designed, using previous experience, to capture a minimum of data on the early severity and management complications of adult severely injured patients – defined as not obeying commands. Interested centres were invited to use the proforma to record information about patients admitted to their centre over a two month period and 67 centres submitted data from just over 1000 patients. The preliminary results were presented at several meetings and confirmed the high commitment to the activities of the Consortium. The data were of high quality and credibility and provided the most up to date picture of the management of severely head injured patients in Western society (EBIC Core Data Study, J. D. Miller Symposium 1996, J Neurotrauma 1997, in press [6]). The centres who participated in the initial survey were subsequently asked to provide data on outcome of reported patients at 6 months after injury. 55 centres (82%) provided information from 835 out of 999 patients (84%) reported by those centres. Full publication is in preparation. Access to information from the study is through Professor G. Murray, University of Edinburgh, the statistician on the Executive of the Consortium.

Guidelines for Management

The evidence gained from previous collaborative studies (Jennett *et al.* 1977 [11]), and supported by recent publications (Murray 1993 [25], Ghajar 1995 [7]), that there are considerable variations in practice in the management of severe head injuries, prompted the development of a set of basic guidelines for use within studies arranged through the Consortium (Mass *et al.*, Acta Neurochirurgica, 1997 [15]). These guidelines were initially drafted in the light of discussions amongst the Executive, were circulated to all interested centres for comment and then revised to take account of this feedback. Although the purposes of this process were to ensure at least a certain minimum standard of management, and to promote consistency between approaches in centres involved in clinical trials, the guidelines developed in this way should be applicable to routine clinical practice. Indeed, these EBIC guidelines evolved by consultation, consensus and a "delphic" process show encouraging close correspondence with guidelines recently

produced by a North American group as a result of a rigorous, evidence-based process (Bullock 1996 [4]).

Clinical Trials

Discussions about potential clinical trials in head injury have been held between the Executive and representatives of several pharmaceutical companies. These have led, so far, to the initiation of two Phase III studies and two Phase II studies. The Consortium has provided "one door" access to expertise and advice about research on the treatment of severe head injuries in Europe, with particular inputs to the design, conduct and analysis of studies and in the selection of centres. This arrangement optimises the chances of a study being successful and influential but can, of course, carry no guarantee of patient recruitment rates or of results. To a participating centre, the arrangement has advantages that the proposed study has been scrutinised and designed in accord with the highest levels of scientific principle and practical experience. Some potential studies have not been proceeded with, often for reasons more related to company policy decisions than scientific or clinical potential, but the arrangement can minimize the risk of unrewarded effort being expended in preparing for a study that does not come to fruition.

The Consortium's primary concern is with the concepts and conduct of a study. Its level of practical involvement during a study varies according to the needs of the study, sponsor and centres. The services EBIC provides include the nomination of members of steering/management committees, safety and efficacy monitoring committees, data analysis and writing committees, the monitoring of activity and trial recruitment in individual centres through "screening logs", review of individual cases for clinical quality, centralised interpretation of CT scans and reports of adverse events. A 24 hour "help line" is available for advice on difficult decisions about entry of individual patients. "Active" centres have been visited by members of the Executive and a detailed database of their facilities and practical methods compiled as a basis for advising sponsors on suitability for studies involving different degrees of expertise and technical complexity.

Communication and Information

Communication and collaboration with the North American Brain Injury Consortium was begun before the formal establishment of EBIC and has been maintained through regular contacts and the attendance of representatives from each organisation at meetings of its counterpart. This has enabled the adoption on either side of the Atlantic of detailed protocols, with minimal change, devised on the other. It has also facilitated a consistency of approach and advice in interaction with sponsoring organisations. Recently, in order to enhance dissemination of knowledge of the existence of the Consortium and its nature, a "web site" has been established:
(http://www.ed.ac.uk/~gdm/EBIC/).

The Future

The level of activity and influence achieved by EBIC in its first two years are reasons for considerable satisfaction. Fears at one time that it might be stillborn have been dispelled but its continued survival and development requires that challenges are faced. The activities of both the central organisational structure and individual centres demand continuing resourcing. The attractiveness of the advice of EBIC to sponsors does not seem to be in doubt; what cannot be foreseen is the extent to which financial management in industry will respond to the advice of clinical scientific project teams, either in pursuing research in head injury or conducting this through EBIC. The benefits of multinational research groups are being recognised by governmental sources of support and these need to be harnessed to sustain the structure and scientific activities of the Consortium.

The list of centres expressing an interest in the Consortium, and in particular those who are "active" is not evenly distributed throughout Europe. At present, activity reflects the historical development of the Consortium largely in North-west European countries. Whether the existing distribution also reflects levels of the expertise, experience and commitment to head injury research remains to be discovered. One of the aims of the Executive is to expand activities more widely, how this can be achieved will be determined not only by the enthusiasm and contribution of potential new centres, but also the availability of new funding. Conversely, there is clearly a wide range of level of activity in existing "active" centres. For example, in the Consortium's major current study (SAPHIR Project) more than 36% of patients recruited so far come from only 13% of centres. This might give reason to question if all existing active centres should remain so, but the information available to the Executive has often provided reasons for understanding

Appendix 1. *The European Brain Injury Consortium European Centres*

Austria
Klagenfurt
Salzburg-Algen
Belgium
Brussels
*Gent
*Leuven
Croatia
Rijeka
Denmark
*Aalborg
*Copenhagen
Eire
*Dublin
Finland
*Helsinki
France
Bordeaux
Marseilles
*Montpellier
*Paris
*Poitiers
*Reims
*Strasbourg
*Toulouse
Germany
Marburg
*München
*Münster
*Murnau/Obb
*Ravensburg
*Regensburg
*Wiesbaden
*Würzburg
Greece
Iraklion
Thessaloniki
Hungary
Pecs
Italy
Ancona
Bologna
Bozen
*Brescia
*Cesena
Ferrara
*Milan
*Monza
*Parma
*Pavia
*Rome
*Treviso
Iasi
Timisoara
Spain
*Barcelona
*Bilbao
*Madrid
Oviedo
*Santander
Sweden
Gothenburg
*Linkoping
*Lund
*Stockholm
*Umea
*Uppsala
Switzerland
*Aarau
*Basle
*Berne
*Lausanne
*Zürich
Turkey
Erzurum
Istanbul
UK
Belfast
Augsburg
*Berlin
*Bielefeld
Bochum
*Bonn
Dortmund
*Dresden
*Duisburg
*Düsseldorf
*Essen
*Erlangen
Frankfurt
*Giessen
*Göttingen
*Greifswald
*Günzburg
*Hamburg
*Hannover
Heidelberg
*Homburg
*Jena
Kiel
*Köln
Lübek
Mainz
*Mannheim
*Turin
*Verona
The Netherlands
*Amsterdam
Den Haag
*Groningen
Heerlen
*Rotterdam
Tilburg
*Utrecht
Norway
*Bergen
*Trondheim
Poland
Krakow
Lublin
Poznan
Szszecin
Warsaw
Wroclaw
Zgierz
Portugal
Porto
Romania
Bucharest
Cluj-Napoca
*Birmingham
*Bristol
*Cambridge
*Cardiff
*Couventry
*Dundee
*Edinburgh
*Glasgow
*Hull
*Leeds
*Liverpool
*London
*Manchester
*Middlesbrough
*Newcastle
*Nottingham
*Plymouth
*Preston
*Salford
*Southampton
*Swansea
Yugoslavia
*Belgrade

* Denotes "active" centre.

why short term local difficulties in facilities may have temporarily limited patient activity. Conversely, the involvement and support of new investigators in previously unknown centres has often been rewarded by a high level of performance in terms of quality and quantity of activity.

Clearly, the Consortium must continue to evolve. This principle is promoted in the constitution of the Executive, some of whose original members have recently retired after playing crucial roles in its formation, and with their replacement the Executive has changed and expanded its representation. At the same time, the structure of the Consortium should enable it to cope with fluctuations in the level of interest and activity in individual centres, especially to incorporate the new participants who will be necessary to bring the vigour and innovation that will be essential for it to continue to flourish.

Acknowledgement

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